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Assessment of risk factors for recurrence of febrile convulsion and subsequent epilepsy in children with febrile seizures

Childhood febrile seizures

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Abstract
Aim: Febrile seizure (FS) is the most common type of convulsion seen in children, and the prognosis for FSs is quite good. However, families and physicians continue to be concerned about the risk of recurrences and development of epilepsy in children in the future. In this study, we aimed to determine the demographic, clinical and laboratory characteristics of children with FSs and risk factors for FS recurrence and epilepsy, as well as to contribute to the accumulation of knowledge on this subject.
Material and Methods: The study included 159 patients who were hospitalized with a diagnosis of FS. Demographic, clinical and laboratory data were recorded from the patients' files. These patients were followed up for at least three years after discharge.
Results: The mean age of the children with FS was 23.9 ± 16.5 months, and the male/female ratio was 1.14/1. The first FS in children was most frequently observed at under 2 years of age (90.6%). Of the 159 cases, 142 were simple FSs and 17 were complex FSs. Recurrence was present in 60 of the patients (37.7%). A significant relationship was revealed between the presence of FSs in families and these recurrences. Epilepsy developed in eight patients (5%). There was a significant relationship between the development of epilepsy and complex FSs and the presence of epilepsy in patients' families.
Discussion: The results of our study show that follow-up of patients with FS seems to be important because of its high recurrence rate and the high risk of epilepsy compared to the general population.

Keywords
Children, Epilepsy, Febrile Seizure, Outcome, Prognosis, Recurrence

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Introduction

Febrile seizure (FS) is the most common type of convulsion seen in children and one of the most frequent neurological disorders in childhood. FS is generally a benign disorder. Studies have reported that the frequency of FSs is 2–10%, and the risk of developing epilepsy after FSs is higher than in the normal population (2–7%) [1-4]. Recurrence occurs in approximately 1/3 of patients.

During the first FS, most families worry that their children will die or will be permanently affected, and also wonder about the fate of their children over the long term. If physicians are to be able to provide satisfactory answers that will relieve the anxieties of these families, they should be able to make predictions based on the demographic, clinical and laboratory characteristics at the time of admission. For such predictions to occur, it is imperative to share knowledge and experience about this subject.

Therefore, to contribute to the knowledge of the subject and to identify recurrences of FSs and the risks of developing epilepsy in these patients, we aimed to determine the demographic, clinical and laboratory characteristics of patients with FS.

Material and Methods

This retrospective study included 159 children who were admitted to the pediatric clinic at the Education and Research Hospital at Adiyaman University's School of Medicine from September 1, 2015 to August 30, 2016. Diagnoses of FS were made based on criteria according to which seizures typically occur in children 6 months to 5 years of age in association with a fever greater than 38°C, who do not have evidence of an intracranial cause, another definable cause of seizure, or a history of afebrile seizure [5]. Convulsions lasting more than 15 minutes, focal, or repetitive within 24 hours were regarded as complicated FS.

The files were scanned in detail for information on socio-demographic characteristics such as gender, age, educational level of the family, number of siblings and their health, history of FS and epilepsy in the family, clinical features such as the starting ages of FS, any disease accompanying FS, neuromotor development status, the frequency of FS, laboratory findings, FS and epilepsy risk factors, the number of convulsions passed up to the time of admission and electroencephalograms (EEG) results. Results were evaluated for all patients after tests, including whole blood counts, glucose, sodium, potassium, chlorine, calcium, phosphorus, magnesium, urea, creatinine, alanine aminotransferase (ALT), aspartate amino transferase (AST), serum iron, iron binding capacity and ferritin levels, urine analysis, and urine cultures.

For this retrospective study, approval was obtained from the Medical Faculty Biomedical Ethics Board (approval date: 18.10.2016, approval number: 2016/6-3) . The files were taken from the archives and evaluated with the approval of the chief physician. The study was conducted in accordance with the Declaration of Helsinki.

The statistical analysis SPSS (Statistical Package for the Social Sciences) 21 for Windows 10.0 program was used during the study. Descriptive statistical methods (mean, standard deviation, and frequency distributions) were used to evaluate the data, the Chi-square test and the Fisher'sexact test were used for comparison of categorical variables; $p< 0.05$ was considered statistically significant.

Results

The study included 159 children, 53.4% of whom were male and 46.6% female. The mean age of the patients was 23.9±16.5 months (range: 6 months–5 years). Considering the age distribution of cases, 28.3% were under 12 months of age, 33.3% were 12–24 months, 23.9% were 24–36 months, 5% were 36–48 months, and 9.4% were over 48 months. The average age of the first FS was 20.88 ± 8.59 months (5–36 months). There was consanguinity between the parents in 32 cases (20.1%), while in 127 cases (79.9%) there was no consanguinity. In 6.3% of the cases, there was a history of FS in the family. In addition, 16 patients (10%) had siblings who had not survived because of miscarriage, and 5 patients (3.1%) had siblings who had died for other reasons. The files that were examined also contained information about the levels of education of 64 mothers and 70 fathers (Table 1).

Rectally examined body temperature levels of children with febrile convulsions ranged from 36.6 degrees Celsius (°C) to 39.9°C, and the mean value was 38.3 ± 0.64°C at emergency room admission. There were 28 children (17.6%) with body temperature measurements below 38°C; 71 children (44.7%) with temperatures between 38 and 38.5°C; 48 children (30.1%) with temperatures between 38.5 and 39°C; and there were 12 children (7.5 %) with temperatures at 39°C above. There were patients whose fever was below 38°C at the time of admission

Table 1. Demographic characteristics of patients

Parameters		n	%
Age (month)	<12	45	28.3
	12.24	53	33.3
	24-36	38	23.9
	36-48	8	5
	≥ 48	15	9.4
Gender	Female	74	46.6
	Male	85	53.4
Family history of febrile seizures	No	149	93.7
	Yes	10	6.3
Gestational age	Preterm	21	13,2
	Term	138	86,8
	Postterm	-	-
Consanguinity between the parents	No	127	79,9
	Yes	32	20,1
Mother's education levels *	Illiterate	4	6,2
	Primary school	35	54,7
	Secondary school	11	17,2
	High school	14	21,9
	University	-	-
Father's education levels *	Illiterate	2	2.9
	Primary school	9	12,8
	Secondary school	4	5,7
	High school	42	60
	University	13	18,6

* Patient files only contain information about the education level of 64 mothers.
** In the patient files, only 70 father's education level information is available.

Table 2. Factors that may be related to recurrence

Parameters		Recurrence (+) n (%)	Recurrence (-) n (%)	p
Gender	Male	29 (48.3)	56 (56.5)	0,308
	Female	31 (51.7)	43 (43.5)	
Age at the first FS (years)	<1	32 (53.3)	25 (25.3)	0,605
	1.2	26 (43.3)	36 (36.4)	
	>2	2 (3.4)	38 (38.3)	
Family history of febrile seizures	Yes	9 (15)	1 (1.1)	0,02
	No	51 (85)	98 (98.9)	
Family history of epilepsy	Yes	9 (15)	4 (4.1)	0,419
	No	51 (85)	95 (95.9)	
EEG result	Normal	15 (68.2)	18 (81.8)	0,488
	Abnormal	7 (31.8)	4 (18.2)	
Body Temperature at the admission (° C)	>39 °C	8 (13.3)	4 (4.1)	0,16
	≤39 °C	52 (86.7)	95 (95.9)	
Febrile seizures type	Simple	53 (88.3)	89 (89.9)	0,609
	Complex	7 (11.7)	10 (10.1)	

Table 3. Factors that may be related to the development of epilepsy

Parameters		Epilepsy (-) n (%)	Epilepsy (+) n (%)	p
Gender	Male	80 (52.9)	5 (62.5)	0,723
	Female	71 (47.1)	3 (37.5)	
Age at the first FS (years)	<1	60 (39.7)	3 (37.5)	0,798
	1.2	60 (39.7)	4 (50)	
	≥2	31 (20.6)	1 (22.5)	
Febrile seizures type	Simple	138 (91.4)	4 (50)	<0.001
	Complex	13 (8.6)	4 (50)	
EEG result*	Normal	30 (78.9)	3 (33.3)	0,154
	Abnormal	8 (21.1)	3 (66.7)	
Family history of epilepsy	Yes	8 (5.3)	5 (62.5)	0,035
	No	143 (94.7)	3 (37.5)	
The numbers of seizures attack	First	97 (64.2)	2 (25)	0,001
	Second	56 (37.1)	4 (50)	
	Third	3 (1.9)	2 (25))	
	Fourth	1 (0.6)	0 (0)	

* EEG was performed in 44 of all cases and in 6 of 8 cases with epilepsy.

to our emergency department because families had done fever-reducing interventions at home. Eighty-eight cases (55.3%) had upper respiratory tract infections, 53 cases (33.3%) had lower respiratory tract infections, 13 cases (8.2%) had acute gastroenteritis, four cases (2.5%) had urinary tract infections and one case (0.6%) had acute otitis media (AOM).

Biochemical tests (glucose, electrolytes, urea, creatinine, ALT and AST) revealed normal values in all of the patients. Hematologically, hemoglobin, hematocrit, iron, total iron binding capacity and ferritin levels were studied. Iron deficiency anemia was detected in 41 patients (26.5%). One hundred fifty-two patients had c-reactive protein (CRP) results, and 62 of them (40.7%) had high CRP levels for their age. In our study, EEG was performed in all patients with complicated FS and in 27 patients with recurrence (total 44 patients), and abnormal epileptic form activity was detected in 11 patients (multifocal in 5 patients, focal in 3 patients, and generalized in 3 patients). Patients in the emergency room received antipyretics (100%), midazolam (24.5%), phenytoin (16.9%) and phenobarbital (1.26%), respectively.

The number of our simple FS cases was 142 (89.3%), and the number of patients with complicated FS was 17 (10.7%). The statistical significance of many parameters that may be related to the type of febrile convulsion was investigated. There was a significant relationship between the presence of abnormal epileptic form activity in the EEGs and the type of FS (p = 0.04). The patients were followed for at least three years for the development of epilepsy and recurrence. The mean follow-up time was 3.9±1,2 years.

Sixty (37.7%) of 159 children had at least one FS recurrence. Only one recurrence was observed in 55/60 children, whereas 5/60 recurred for a second time. Three recurrences occurred in one child. The statistical significance of many parameters that may be related to recurrence was investigated (Table 2). There was no meaningful relationship between many parameters and recurrence. On the other hand, there was a significant relationship between the presence of a family history of FS and recurrence (p = 0.02).

Epilepsy developed in eight patients (5%). Seven of these patients were diagnosed with generalized tonic-clonic epilepsy, and one was diagnosed with focal myoclonic epilepsy. Levetiracetam was initiated in six patients and valproic acid in 2 patients. The statistical significance of many parameters that may be related to the development of epilepsy was investigated (Table 3). A statistically significant relationship was detected between the type of FS and the development of epilepsy (p < 0.001). No significant correlation was found between the limited number of EEG results and the development of epilepsy (p = 0.154). A statistically significant relationship was found between the presence of epilepsy in the family and the development of epilepsy (p = 0.035). A statistically significant relationship was also found between the number of FS and epilepsy development (p = 0.001). Neurodevelopmental retardation and the duration of fever, which are among the risk factors of epilepsy development after febrile convulsions, could not be evaluated because sufficient information could not be found in the patient files.

Discussion

Febrile seizures are the most common neurological problem in childhood; they are also the most common type of convulsions in children. Although FS usually is a benign disorder, it is significant because of its consequences such as recurrence and epilepsy [5,6]. In this study, it was aimed to discuss useful information for predicting prognosis in patients presenting with FS.

Several studies have reported that FS is more common in male patients [7-8]. In addition, the average age of these patients was determined to be around 20 months. Byeon et al. [4] reported that the age at which the first episode of FS occurred must often was also 18–30 months. Similarly, in our study, the rate of boys was higher than that of girls (53.4%). The average age of our patients was 20.8 months, and 80% of the patients had their first FS attack when they were under two years of age. In many studies, the presence of FS history in the patients' families ranged from 16% to 32% [5-9]. In our study, the

incidence of FS in the family was found to be 6.3%. In children whose families have a high incidence of epilepsy, the incidence of FS is higher than in the normal population. A family history of epilepsy was 5.9% in the study of Canpolat et al [10]. In our study, a family history of epilepsy was found in 8.2% of cases in accordance with the literature.

There are two types of febrile seizures simple and complicated. The complicated FS occurrence rate was found to be 15.8 % and 18.4 % in studies performed by Sharawat et al. [9] and Canpolat et al. [10], respectively. In our study, the complicated FS ratio was found to be 10.7 %. There are a limited number of studies in the literature that examine the factors associated with seizure type. In our study, a single factor associated with seizure type was an EEG abnormality. Although EEGs are often performed in children with FS, their diagnostic value is quite limited. The EEG abnormality was found to be 10 % and 44.6 % in studies performed by Yilmaz et al. [11] and Yucel et al. [12], respectively. EEG abnormalities were more common in patients with complicated FS in all of these studies. Similarly, in our study, EEG abnormalities were found in 25 % of patients, and the frequency of EEG abnormalities was higher in complicated FS.

FS recurs in 30-55 % of children who have had an initial case [13-17]. Although mostly a single recurrence is observed, two, three and more recurrences can be seen. Pavlidou et al. [13] reported that 44.2% of children had at least one FS recurrence. Only one recurrence was reported in 52% of these children, whereas 48% of them recurred for a second time. Additionally, three recurrences occurred in 48 children, and 31 children had four or more recurrences. Numerous factors have been identified associated with these recurrences. Factors that increase the risk of recurrence include: the first seizure is seen under the age of one year, a history of FS in first-degree relatives, low fever during the first FS episode and short duration of fever before the seizure. Bessisso et al. [18] examined the risk factors for recurrence and reported that risk factors for recurrence noted were male sex, and complex febrile seizures. Agrawal et al. [14] found male gender and age <1year to be significant risk factors for recurrences. Tosun et al. [17] reported that a family history of FS was a risk factor for recurrence, but family history of epilepsy was not a significant risk factor for recurrence. A study reported that abnormal EEG was not predictive of febrile seizure recurrence [19]. However, Ojha et al. [16] stated that low temperature at onset of FS, short duration of fever before the onset of FS, and atypical FS were the risk factors for recurrent FS. In our study, recurrence was observed in 60 (37.7%) patients, and a significant correlation was found between the presence of a family history of FS and recurrence ($p = 0.02$). In addition, two recurrences occurred in 5 children, and from those one child had three recurrences. Although recurrence was more common in patients with several risk factors, these differences were not significant except for the presence of a family history of FS.

Although the risk of epilepsy development after FS is a controversial issue, this risk has increased slightly compared to the general population. In various studies, this risk has been found in rates ranging from 2 to 7%. Several studies reported that risk factors for the development of epilepsy include shorter duration of fever (<1 hour) before the seizure, first-degree relatives have a history of epilepsy, an existing neurological or developmental anomaly before the appearance of FS, complicated FS, an onset of febrile seizures before the age of 1 year or after the age of 3 years and epileptiform discharges on EEG [5,10,13]. Pavlidou et al. [13] reported that positive family history of epilepsy of first- and second-degree relatives was found to be a major prognostic factor for the development of epilepsy after FS. In a recent study, it was reported that the risk of developing epilepsy was 4.5 times higher in children with pathological EEG after FS and 21.1 times higher in those with neurodevelopmental abnormality [10]. In our study, epilepsy developed in 8 (5%) patients in accordance with the literature. Complicated FS and the presence of epilepsy in the family were significantly associated with an increased risk of the development of epilepsy. As the number of attacks increased, the risk of developing epilepsy increased significantly.

Limitations

The most important limitation of our study is that it was designed retrospectively. Since some data could not be obtained from files, reliable analysis could not be made on some issues. In addition, since there was not enough information in the files about neurodevelopmental retardation and duration of fever before FS episode, which are among the risk factors of epilepsy after FS, comments on this subject could not be made.

Conclusions

The results of our study show that it appears to be important to follow FS patients because of its high recurrence rate and the high risk of epilepsy compared to the general population. Presence of a family history of FS was related to recurrence and complicated FS, a family history of epilepsy and a high number of FS episodes were found to be associated with the development of epilepsy.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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